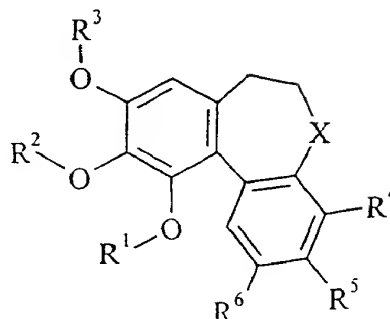


CLAIMS

1. The use of a compound of the formula I:



(I)

wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy, -OR⁸ or -

- 10 NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following nine groups:

1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined herein, or
15 phenyl,

(which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

20 Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋

25 ,aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋

,alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms,

selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)),

C₁₋₄alkylZ¹ (wherein Z¹ is as defined herein), and

a group -Y²R¹³ (wherein Y² is -NR¹⁴C(O)- or -O-C(O)- (wherein R¹⁴ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹³ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R¹⁵ wherein R¹⁵ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR¹⁶R¹⁷ and -NR¹⁸COR¹⁹ (wherein R¹⁶, R¹⁷, R¹⁸ and R¹⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)));

2) R¹⁵ wherein R¹⁵ is as defined herein;

3) C₂₋₇alkenylR¹⁵ (wherein R¹⁵ is as defined herein);

4) C₃₋₇alkynylR¹⁵ (wherein R¹⁵ is as defined herein));

5) Z¹ (wherein Z¹ is as defined herein);

6) C₁₋₇alkylZ¹ (wherein Z¹ is as defined herein);

7) C₁₋₇alkylY⁸Z¹ (wherein Z¹ is as defined herein and Y⁸ is -C(O)-, -NR⁵⁹C(O)-, -NR⁵⁹C(O)C₁₋₄alkyl-, -C(O)NR⁶⁰- or -C(O)NR⁶⁰C₁₋₄alkyl-, (wherein R⁵⁹ and R⁶⁰, which may be the same or different, each represents hydrogen, C₁₋₃alkyl, C₁₋₃hydroxyalkyl or C₁₋₃alkoxyC₂₋₃alkyl));

8) (C₁₋₇alkyl)_cY⁹Z³ (wherein c is 0 or 1, Z³ is an amino acid group and Y⁹ is a direct bond, -C(O)- or -NR⁶¹- (wherein R⁶¹ is hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl)); and

9) C₁₋₇alkylR¹⁵ (wherein R¹⁵ is as defined herein);

and R⁹ is hydrogen, C₁₋₇alkyl or C₃₋₇cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C₁₋₄alkoxy and phenyl);

R¹, R² and R³ are each independently

hydrogen, PO_3H_2 , sulphate, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, a group $\text{R}^{20}\text{C}_{1-7}$ alkyl (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy), C_{1-7} alkyl or C_{1-7} alkylsulphonyl

(which alkyl or alkylsulphonyl group may bear one or more substituents selected from:

- 5 halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-\text{Y}^2\text{R}^{21}$ (wherein Y^2 is $-\text{NR}^{22}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{22} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{21} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{23} wherein R^{23} is a phenyl group or a 5-10-membered
- 10 aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{24}\text{R}^{25}$ and $-\text{NR}^{26}\text{COR}^{27}$ (wherein R^{24} , R^{25} , R^{26} and R^{27} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 15

with the proviso that at least two of R^1 , R^2 and R^3 are C_{1-7} alkyl;

R^4 , R^5 and R^6 are each independently selected from:

- 20 hydrogen, $-\text{OPO}_3\text{H}_2$, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} thioalkoxy, C_{1-7} alkyl,
- (which alkyl group may bear one or more substituents selected from:
- halogeno, amino, C_{1-4} alkylamino, $\text{di}(\text{C}_{1-4}$ alkyl)amino, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy,
- 25 phenyl, sulphate, phosphate and a group $-\text{Y}^3\text{R}^{28}$ (wherein Y^3 is $-\text{NR}^{29}\text{C}(\text{O})-$ or $-\text{O}-\text{C}(\text{O})-$ (wherein R^{29} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{28} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{30} wherein R^{30} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear
- 30 one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{31}\text{R}^{32}$ and $-\text{NR}^{31}\text{COR}^{32}$ (wherein R^{31} , R^{32} , R^{33} and

R^{34} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)), and

a group $-Y^4R^{35}$

(wherein Y^4 is $-C(O)-$, $-OC(O)-$, $-O-$, $-SO-$, $-SO_2-$, $-OSO_2-$, $-NR^{36}-$, $-C_{1-4}$ alkyl $NR^{36}-$, $-C_{1-4}$ alkyl $C(O)-$, $-NR^{37}C(O)-$, $-OC(O)O-$, $-C(O)NR^{38}-$ or $-NR^{39}C(O)O-$ (wherein R^{36} , R^{37} , R^{38} and R^{39} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} alkylamino, di(C_{1-7} alkyl)amino, amino C_{1-7} alkylamino, C_{1-7} alkylamino C_{1-7} alkylamino, C_{1-7} alkanoylamino C_{1-7} alkyl, di(C_{1-7} alkyl)amino C_{1-7} alkylamino, C_{1-7} alkylphosphate, C_{1-7} alkylphosphonate, C_{1-7} alkylcarbamoyl C_{1-7} alkyl,

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino, alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

halogeno, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkylsulphanyl, C_{1-4} alkylsulphonyl, C_{1-4} alkoxycarbonylamino, C_{1-4} alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group $-Y^5R^{40}$ (wherein Y^5 is $-NR^{41}C(O)-$, $-C(O)NR^{42}-$, $-C(O)-O-$ or $-O-C(O)-$ (wherein R^{41} and R^{42} which may be the same or different each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, carboxy C_{1-7} alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{44}R^{45}$ and $-NR^{46}COR^{47}$ (wherein R^{44} , R^{45} , R^{46} and R^{47} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected

independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from

hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, di(C₁₋₄hydroxyalkyl)aminoC₁₋₄alkyl, di(C₁₋₄aminoalkyl)aminoC₁₋₄alkyl, C₁₋₄hydroxyalkoxy, carboxy, C₁₋₄carboxyalkyl, phenyl, cyano, -CONR⁴⁹R⁵⁰, -NR⁵¹COR⁵² (wherein R⁴⁹, R⁵⁰, R⁵¹ and R⁵², which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and C₁₋₄alkylR⁵³ (wherein R⁵³ is as defined herein),

C₁₋₇alkylR⁴⁸ (wherein R⁴⁸ is as defined herein),

R⁵³ (wherein R⁵³ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄carboxyalkyl, C₁₋₄aminoalkyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and R⁵⁴ (wherein R⁵⁴ is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

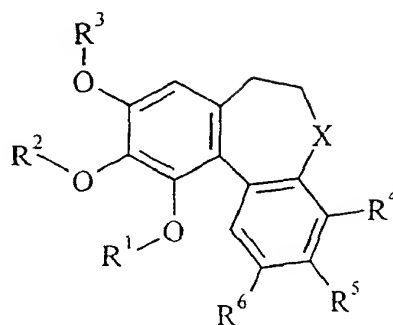
oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkoxyC₁₋₄alkyl and C₁₋₄alkylsulphonylC₁₋₄alkyl)), or

(CH₂)_aY⁶(CH₂)_bR⁵³ (wherein R⁵³ is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y⁶ represents a direct bond, -O-, -C(O)-, -NR⁵⁵-, -NR⁵⁶C(O)- or -C(O)NR⁵⁷- (wherein R⁵⁵, R⁵⁶, and R⁵⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl), and wherein one or more of the (CH₂)_a or (CH₂)_b groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R⁵ is not hydroxy, alkoxy, substituted alkoxy (wherein R⁵ is Y⁴R³⁵ and Y⁴ is -O- and R³⁵ is C₁₋₇alkyl bearing one or more substituents selected from the list given herein), -OPO₃H₂, -O-C₁₋₇alkanoyl or benzyloxy;

or a salt thereof, a pharmaceutically acceptable salt thereof, a solvate or hydrate thereof, or a prodrug thereof in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.

2. A compound of the formula IIa:



(IIa)

5 wherein

X is

-C(O)-, -C(S)-, -C=NOH, or -CH(R⁷)- wherein R⁷ is hydrogen, hydroxy, C₁₋₇alkoxy, -OR⁸ or -NR⁸R⁹ (wherein R⁸ is a group -Y¹R¹⁰ (wherein Y¹ is a direct bond, -C(O)-, -C(S)-, -S-, -C(O)O-, -C(O)NR¹¹-, -SO₂- or -SO₂NR¹²- (wherein R¹¹ and R¹², which may be the same or
10 different, each independently represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R¹⁰ is selected from one of the following nine groups:

1) hydrogen, C₁₋₇alkyl, C₃₋₇cycloalkyl, C₁₋₄alkylY⁸C₁₋₄alkyl wherein Y⁸ is as defined herein, or phenyl,

(which alkyl, cycloalkyl, alkylY⁸alkyl or phenyl group may bear one or more substituents
15 selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, carboxy, carbamoyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, phenyl, nitro, sulphate, phosphate,

Z¹ (wherein Z¹ represents a 5-6 membered saturated heterocyclic group (linked via
20 carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C₁₋₄alkyl, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄aminoalkyl, C₁₋₇alkanoyl, cyanoC₁₋₄alkyl, C₁₋₄alkoxyC₁₋₄alkyl, C₁₋₄alkylsulphonylC₁₋₄alkyl and Z² (wherein Z² is a 5-6-membered saturated

heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms,
25 selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl, C_{1-7} alkanoyl, cyano C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl(C_{1-4} alkyl)),

C_{1-4} alkyl Z^1 (wherein Z^1 is as defined herein), and

- 5 a group $-Y^2R^{13}$ (wherein Y^2 is $-NR^{14}C(O)-$ or $-O-C(O)-$ (wherein R^{14} represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{13} is C_{1-7} alkyl, C_{3-7} cycloalkyl or a group R^{15} wherein R^{15} is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more
- 10 substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-CONR^{16}R^{17}$ and $-NR^{18}COR^{19}$ (wherein R^{16} , R^{17} , R^{18} and R^{19} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 15 2) R^{15} wherein R^{15} is as defined herein;
- 3) C_{2-7} alkenyl R^{15} (wherein R^{15} is as defined herein);
- 4) C_{3-7} alkynyl R^{15} (wherein R^{15} is as defined herein));
- 5) Z^1 (wherein Z^1 is as defined herein);
- 6) C_{1-7} alkyl Z^1 (wherein Z^1 is as defined herein);
- 20 7) C_{1-7} alkyl Y^8Z^1 (wherein Z^1 is as defined herein and Y^8 is $-C(O)-$, $-NR^{59}C(O)-$, $-NR^{59}C(O)C_{1-4}$ alkyl-, $-C(O)NR^{60}-$ or $-C(O)NR^{60}C_{1-4}$ alkyl-, (wherein R^{59} and R^{60} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl, C_{1-3} hydroxyalkyl or C_{1-3} alkoxy C_{2-3} alkyl));
- 8) $(C_{1-7}alkyl)_cY^9Z^3$ (wherein c is 0 or 1, Z^3 is an amino acid group and Y^9 is a direct bond, $-C(O)-$ or $-NR^{61}-$ (wherein R^{61} is hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl)); and
- 25 9) C_{1-7} alkyl R^{15} (wherein R^{15} is as defined herein);
- and R^9 is hydrogen, C_{1-7} alkyl or C_{3-7} cycloalkyl, which alkyl or cycloalkyl group may bear one or more substituents selected from C_{1-4} alkoxy and phenyl);
- R^1 , R^2 and R^3 are each independently
- hydrogen, PO_3H_2 , sulphate, C_{3-7} cycloalkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkanoyl, a group
- 30 $R^{20}C_{1-7}alkyl$ (wherein R^{20} is phenyl which may bear one or more substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} aminoalkyl and C_{1-4} hydroxyalkoxy), C_{1-7} alkyl or C_{1-7} alkylsulphonyl (which alkyl or alkylsulphonyl group may bear one or more substituents selected from:

- halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y²R²¹ (wherein Y² is -NR²²C(O)- or -O-C(O)- (wherein R²² represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²¹ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R²³ wherein R²³ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR²⁴R²⁵ and -NR²⁶COR²⁷ (wherein R²⁴, R²⁵, R²⁶ and R²⁷, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- with the proviso that at least two of R¹, R² and R³ are C₁₋₇alkyl;
- R⁴ is
- hydrogen, cyano, halogeno, nitro, amino, hydroxy, C₁₋₇alkoxy, C₁₋₇thioalkoxy, C₁₋₇alkanoyl or C₁₋₇alkyl,
- (which alkyl group may bear one or more substituents selected from:
- halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl));
- R⁵ and R⁶ are each independently selected from
- hydrogen, -OPO₃H₂, phosphonate, cyano, halogeno, nitro, amino, carboxy, carbamoyl, hydroxy, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇thioalkoxy, C₁₋₇alkyl.

(which alkyl group may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, sulphate, phosphate and a group -Y³R²⁸ (wherein Y³ is -NR²⁹C(O)- or -O-C(O)- (wherein R²⁹ represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R²⁸ is C₁₋₇alkyl, C₃₋₇cycloalkyl or a group R³⁰ wherein R³⁰ is a phenyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄alkoxy, C₁₋₄hydroxyalkyl, C₁₋₄aminoalkyl, C₁₋₄alkylamino, C₁₋₄hydroxyalkoxy, carboxy, cyano, -CONR³¹R³² and -NR³¹COR³² (wherein R³¹, R³², R³³ and R³⁴, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl))), and

a group -Y⁴R³⁵

(wherein Y⁴ is -C(O)-, -OC(O)-, -O-, -SO-, -SO₂-, -OSO₂-, -NR³⁶-, -C₁₋₄alkylNR³⁶-, -C₁₋₄alkylC(O)-, -NR³⁷C(O)-, -OC(O)O-, -C(O)NR³⁸- or -NR³⁹C(O)O- (wherein R³⁶, R³⁷, R³⁸ and R³⁹, which may be the same or different, each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and R³⁵ is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, sulphate, hydroxy, amino, C₁₋₇alkyl, C₁₋₇alkoxy, C₁₋₇alkanoyl, C₁₋₇alkylamino, di(C₁₋₇alkyl)amino, aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, C₁₋₇alkanoylaminoC₁₋₇alkyl, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino, C₁₋₇alkylphosphate, C₁₋₇alkylphosphonate, C₁₋₇alkylcarbamoylC₁₋₇alkyl,

(which alkyl, alkoxy, alkanoyl, alkylamino, dialkylamino, aminoalkylamino,

alkylaminoalkylamino, alkanoylaminoalkyl, dialkylaminoalkylamino, alkylphosphate, alkylphosphonate or alkylcarbamoylalkyl, may bear one or more substituents selected from:

halogeno, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, hydroxy, C₁₋₄hydroxyalkyl, C₁₋₄alkoxy, C₁₋₄alkylsulphanyl, C₁₋₄alkylsulphonyl, C₁₋₄alkoxycarbonylamino, C₁₋₄alkanoyl, carboxy, phenyl, nitro, sulphate, phosphate and a group -Y⁵R⁴⁰ (wherein Y⁵ is -NR⁴¹C(O)-, -C(O)NR⁴²-, -C(O)-O- or -O-C(O)- (wherein R⁴¹ and R⁴² which may be the same or different each represents hydrogen, C₁₋₃alkyl or C₁₋₃alkoxyC₂₋₃alkyl) and

- R^{40} is C_{1-7} alkyl, C_{3-7} cycloalkyl, carboxy C_{1-7} alkyl or a group R^{43} wherein R^{43} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, C_{1-4} hydroxyalkoxy, carboxy, cyano, $-\text{CONR}^{44}\text{R}^{45}$ and $-\text{NR}^{46}\text{COR}^{47}$ (wherein R^{44} , R^{45} , R^{46} and R^{47} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl))),
- R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may bear one or more substituents selected from hydroxy, nitro, halogeno, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino C_{1-4} alkyl, di(C_{1-4} hydroxyalkyl)amino C_{1-4} alkyl, di(C_{1-4} aminoalkyl)amino C_{1-4} alkyl, C_{1-4} hydroxyalkoxy, carboxy, C_{1-4} carboxyalkyl, phenyl, cyano, $-\text{CONR}^{49}\text{R}^{50}$, $-\text{NR}^{51}\text{COR}^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and C_{1-4} alkyl R^{53} (wherein R^{53} is as defined herein),
- C_{1-7} alkyl R^{48} (wherein R^{48} is as defined herein),
- R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} carboxyalkyl, C_{1-4} aminoalkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl C_{1-4} alkyl)), or
- $(\text{CH}_2)_a\text{Y}^6(\text{CH}_2)_b\text{R}^{53}$ (wherein R^{53} is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y^6 represents a direct bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{NR}^{55}-$, $-\text{NR}^{56}\text{C}(\text{O})-$ or -

$C(O)NR^{57}$ - (wherein R^{55} , R^{56} , and R^{57} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and wherein one or more of the $(CH_2)_a$ or $(CH_2)_b$ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

- 5 with the proviso that R^5 is not hydroxy, alkoxy, substituted alkoxy (wherein R^5 is Y^4R^{35} and Y^4 is -O- and R^{35} is C_{1-7} alkyl bearing one or more substituents selected from the list given herein), - OPO_3H_2 , - $O-C_{1-7}$ alkanoyl or benzyloxy;

with the further proviso that at least one of R^5 or R^6 is a group $-Y^4R^{35}$ (wherein Y^4 and R^{35} are as defined herein) but with the further provisos

- 10 that when R^5 is $-Y^4R^{35}$ and R^6 is hydrogen, hydroxy, methoxy or methoxycarbonyl, $-Y^4R^{35}$ is not selected from cases wherein:

Y^4 is - $C(O)-$, - $OC(O)-$, -O-, - $SO-$, - OSO_2- , - $NR^{36}-$, - $NR^{37}C(O)-$ or - $C(O)NR^{38}-$ (wherein R^{36} , R^{37} and R^{38} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and R^{35} is

- 15 a glycine, valine or lysine group, a dipeptide of glycine and valine groups, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl,

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno, hydroxy, and a group $-Y^5R^{40}$ (wherein Y^5 is - $O-C(O)-$ and R^{40} is C_{1-7} alkyl)), or

- 20 R^{48} (wherein R^{48} is a tetrazolyl group (which may or may not be substituted as herein defined), a phenyl group or a benzyl group which phenyl or benzyl group may bear one or more substituents selected from C_{1-4} alkyl); and

that when R^6 is $-Y^4R^{35}$ and R^5 is hydrogen, hydroxy, methoxy or methoxycarbonyl, $-Y^4R^{35}$ is not selected from cases wherein:

- 25 Y^4 is - $C(O)-$, -O- or - OSO_2- and R^{35} is C_{1-7} alkyl, C_{1-7} alkoxy

(which alkyl, alkoxy or alkanoyl may bear one or more substituents selected from: halogeno),

- 30 R^{48} (wherein R^{48} is a benzyl group which benzyl group may bear one or more substituents selected from C_{1-4} alkyl), or

R^{53} (wherein R^{53} is piperidiny);

or a salt thereof.

3. The use of a compound of the formula IIa as defined in claim 2, or a salt thereof, a pharmaceutically acceptable salt thereof, a solvate or hydrate thereof, or a prodrug thereof, in the manufacture of a medicament for use in the production of a vascular damaging effect in warm-blooded animals such as humans.
4. A compound according to claim 2 wherein X is $-\text{CH}(\text{R}^7)-$ wherein R^7 is $-\text{OR}^8$ or $-\text{NR}^8\text{R}^9$ (wherein R^8 is a group $-\text{Y}^1\text{R}^{10}$ (wherein Y^1 is $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$ or $-\text{C}(\text{O})\text{NR}^{11}-$ (wherein R^{11} represents hydrogen, $\text{C}_{1-3}\text{alkyl}$ or $\text{C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$) and R^{10} is as defined in claim 2) and R^9 is as defined in claim 2).
5. A compound according to claim 2 or claim 4 wherein R^1 , R^2 and R^3 are each methyl.
6. A compound according to any one of claims 2, 4 or 5 wherein R^4 is hydrogen.
7. A compound according to any one of claims 2, 4, 5 or 6 wherein R^6 is hydrogen, halogeno, amino, carboxy, hydroxy, $\text{C}_{1-7}\text{alkoxy}$ or a group Y^4R^{35} (wherein Y^4 is $-\text{C}(\text{O})-$, $-\text{O}-$ or $-\text{OSO}_2-$ and R^{35} is $\text{C}_{1-7}\text{alkyl}$, $\text{C}_{1-7}\text{alkoxy}$ (which alkyl or alkoxy may bear one or more substituents selected from halogeno), R^{48} (wherein R^{48} is a benzyl group) or R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms selected independently from O, S and N)).
8. A compound according to any one of claims 2, 4, 5, 6 or 7 wherein R^6 is hydrogen, $\text{C}(\text{O})\text{OCH}_3$ or methoxy.
9. A compound according to any one of claims 2, 4, 5, 6, 7 or 8 wherein R^5 is hydrogen, halogeno, amino, carboxy, carbamoyl, $\text{C}_{1-7}\text{alkanoyl}$, $\text{C}_{1-7}\text{thioalkoxy}$, or a group $-\text{Y}^4\text{R}^{35}$ (wherein Y^4 is $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{O}-$, $-\text{SO}-$, $-\text{OSO}_2-$, $-\text{NR}^{36}-$, $-\text{NR}^{37}\text{C}(\text{O})-$ or $-\text{C}(\text{O})\text{NR}^{38}-$ (wherein R^{36} , R^{37} and R^{38} , which may be the same or different, each represents hydrogen, $\text{C}_{1-3}\text{alkyl}$ or $\text{C}_{1-3}\text{alkoxyC}_{2-3}\text{alkyl}$) and

*Cont
Al*

R^{35} is a sugar moiety, a mono-peptide, a di-peptide, a tri-peptide, a tetra-peptide, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkanoyl, C_{1-7} alkanoylamino C_{1-7} alkyl,

(which alkyl, alkoxy, alkanoyl, alkanoylaminoalkyl may bear one or more substituents selected from:

5 halogeno, amino, hydroxy, carboxy, and a group $-Y^5R^{40}$ (wherein Y^5 is $-C(O)-O-$ or $-O-C(O)-$ and R^{40} is C_{1-7} alkyl or a group R^{43} wherein R^{43} is a benzyl group),

R^{48} (wherein R^{48} is a phenyl group, a benzyl group or a 5-10-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-4 heteroatoms selected independently from O, N and S, which phenyl, benzyl or aromatic heterocyclic group may

10 bear one or more substituents selected from

hydroxy, fluoro, amino, C_{1-4} alkoxy, C_{1-4} hydroxyalkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino C_{1-4} alkyl, di(C_{1-4} hydroxyalkyl)amino C_{1-4} alkyl, di(C_{1-4} aminoalkyl)amino C_{1-4} alkyl, C_{1-4} hydroxyalkoxy, carboxy, C_{1-4} carboxyalkyl, cyano, $-CONR^{49}R^{50}$, $-NR^{51}COR^{52}$ (wherein R^{49} , R^{50} , R^{51} and R^{52} , which may be the

15 same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl) and C_{1-4} alkyl R^{53} (wherein R^{53} is as defined herein),

C_{1-7} alkyl R^{48} (wherein R^{48} is as defined herein),

R^{53} (wherein R^{53} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which

20 heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, fluoro, chloro, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} carboxyalkyl, C_{1-4} aminoalkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} alkylsulphonyl C_{1-4} alkyl and R^{54} (wherein R^{54} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N,

25 which heterocyclic group may bear 1 or 2 substituents selected from

oxo, hydroxy, halogeno, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl and C_{1-4} alkylsulphonyl(C_{1-4} alkyl)), or

$(CH_2)_aY^6(CH_2)_bR^{53}$ (wherein R^{53} is as defined herein, a is 0, or an integer 1-4, b is 0 or an integer 1-4 and Y^6 represents a direct bond, $-O-$, $-C(O)-$, $-NR^{55}-$, $-NR^{56}C(O)-$ or

30 $C(O)NR^{57}-$ (wherein R^{55} , R^{56} , and R^{57} , which may be the same or different, each represents hydrogen, C_{1-3} alkyl or C_{1-3} alkoxy C_{2-3} alkyl), and wherein one or more of the $(CH_2)_a$ or

(CH₂)₆ groups may bear one or more substituents selected from hydroxy, amino and halogeno));

with the proviso that R⁵ is not alkoxy, substituted alkoxy (wherein R⁵ is Y⁴R³⁵ and Y⁴ is -O- and R³⁵ is C₁₋₇alkyl bearing one or more substituents selected from the list given herein), -O-

5 C₁₋₇alkanoyl or benzyloxy.

10. A compound according to claim 2 selected from:

(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-
{[(2*R*)-2,6-diaminohexanoyl]amino} propanoate,

10 (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[(2-
aminoacetyl)amino]propanoate,

N-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-
yl]oxymethyl)-2-morpholinoacetamide,

(2*S*,3*S*,4*S*,5*R*,6*R*)-6-([(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
15 dibenzo[*a,c*]cyclohepten-3-yl]oxy)-3,4,5-trihydroxytetrahydro-2*H*-pyran-2-carboxylic acid,
N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-
dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

N-[(5*S*)-3-(4-{morpholinomethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-dihydro-5*H*-
dibenzo[*a,c*]cyclohepten-5-yl]acetamide,

20 (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl 3-[4-
methylpiperazin-1-ylcarbonyl]propanoate,

5-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-
yl]oxycarbonyl]pentanoic acid,

4-(3-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-
25 yl]oxy-3-oxopropyl)benzoic acid and

(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-
yl]-2-amino-3-hydroxypropanamide,

and salts thereof.

30 11. A compound according to claim 2 selected from

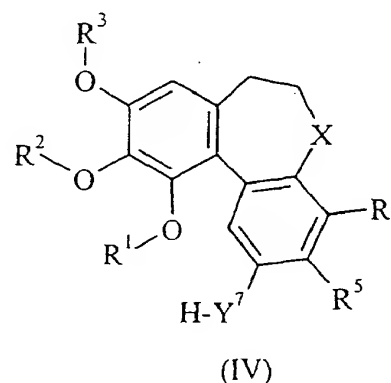
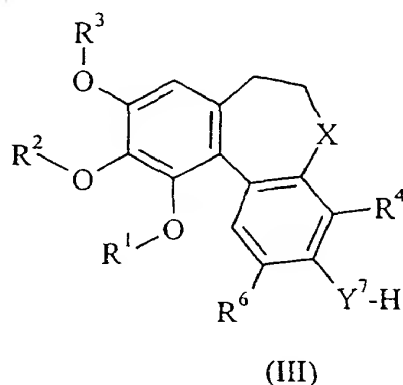
N-[(5*S*)-3-(4-{4-methylpiperazin-1-ylmethyl}phenylcarbonyloxy)-9,10,11-trimethoxy-6,7-
dihydro-5*H*-dibenzo[*a,c*]cyclohepten-5-yl]acetamide and

(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-3-hydroxypropanamide,
and salts thereof.

- 5 12. A compound according to claim 2 selected from
(2*S*)-*N*-[(5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a,c*]cyclohepten-3-yl]-2-amino-5-[(2-nitroethanimidoyl)amino]pentanamide
and salts thereof.

- 10 13. A process for the manufacture of a compound of formula IIa as defined in claim 2 which comprises:

(a) for the preparation of compounds of formula IIa and salts thereof in which R⁵ or R⁶ is a group Y⁴R³⁵ (wherein R³⁵ is as defined in claim 2 and Y⁴ is a group -OC(O)- or -NHC(O)-), the reaction of a compound of formula III or IV:



15

(wherein X, R¹, R², R³, R⁴, R⁵, R⁶ are as defined in claim 2 and Y⁷ is -O- or -NH-), by acylation or coupling reactions;

- 20 (b) for the preparation of compounds of formula IIa and salts thereof in which R⁵ or R⁶ is a group Y⁴R³⁵ (wherein R³⁵ is C₁₋₇alkoxy which may be substituted as defined in claim 2 and Y⁴ is a group -OC(O)- or -NHC(O)-), the reaction of a compound of formula III and IV, by acylation reactions;
- (c) for the preparation of compounds of formula IIa and salts thereof in which R⁵ or R⁶ is a
25 group Y⁴R³⁵ (wherein R³⁵ is aminoC₁₋₇alkylamino, C₁₋₇alkylaminoC₁₋₇alkylamino, di(C₁₋₇alkyl)aminoC₁₋₇alkylamino and may be substituted as defined in claim 2, or is R⁵³ (wherein

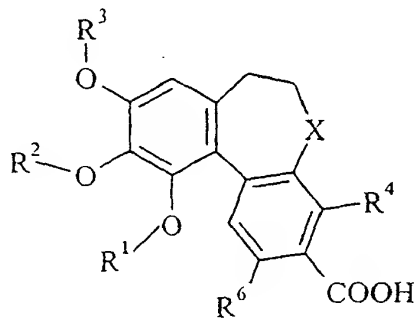
R^{53} is as defined in claim 2) and Y^4 is a group $-OC(O)-$ or $-NHC(O)-$, can be prepared by the reaction of a compound of formula III or IV, acylation reactions;

(d) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is a sugar moiety and Y^4 is a group $-O-$ or $-NH-$), the reaction of a compound of formula III or IV, glycosylation reactions;

(e) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is sulphate and Y^4 is a group $-O-$ or $-NH-$), the reaction of a compound of formula III or IV, by sulphonylation reactions;

(f) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is a group Y^4R^{35} (wherein R^{35} is C_{1-7} alkylphosphate and may be substituted as defined in claim 2 and Y^4 is a group $-O-$ or $-NH-$), the reaction of a compound of formula III or IV, by phosphorylation reactions;

(g) for the preparation of compounds of formula IIa and salts thereof in which R^5 is amino the reaction of a carboxylic acid of formula V:



(V)

(wherein X, R^1 , R^2 , R^3 , R^4 and R^6 are as defined in claim 2) via Curtius rearrangement and hydrolysis; and

(h) for the preparation of compounds of formula IIa and salts thereof in which R^5 or R^6 is chloro the reaction of a compound of formula III or IV by the Sandmeyer reaction; and when a pharmaceutically acceptable salt of a compound of formula IIa is required, reaction of the compound obtained with an acid or base whereby to obtain the desired pharmaceutically acceptable salt.

14. A pharmaceutical composition which comprises as active ingredient a compound of formula IIa as defined in claim 2 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient or carrier.
- 5 15. A method for producing a vascular damaging effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula IIa or a pharmaceutically acceptable salt thereof as defined in claim 2.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000